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STUDIES ON ARGENTINE PLANTS—XXII[1]

HELIETTIN, A NEW FUROCOUMARIN FROM *HELIETTA LONGIFOLIATA* BRITT.[2]

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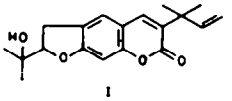
Abstract—A new terpenic furocoumarin was isolated from the bark of *Helietta longifoliata* Britt. It was named *heliettin*, and its structure established as (±)-3-(1,1-dimethylallyl)-6,7-dihydro-7-(1-hydroxy-1-methylethyl)-2H-furo-[2,3-g]-1-benzopyran-2-one (I), by spectral studies and chemical evidence.

Helietta longifoliata Britt. (Rutaceae) is a fair-sized tree that grows in the tropical forest of northeast Argentina. There is no record in the literature of chemical investigation on the genus *Helietta*.

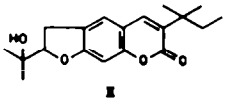
From the petroleum ether extract of the ground bark, a fluorescent crystalline precipitate was obtained which was identified as a new furocoumarin with structure I, and named *heliettin*.

Heliettin (I), m.p. 165·5–166°, $[\alpha]_D^{20}$ ±0·0°, analyzed for the molecular formula $C_{19}H_{22}O_4$. The UV spectrum shows a max at 330 mμ (log ε 4·30). The IR spectrum has the following important bands: 3500 cm^{-1} (OH), 1710 and 1630 cm^{-1} (conjugated lactone), 1580 cm^{-1} (aromatic). The NMR spectrum (Fig. 3) will be analyzed later.

Heliettin, hydrogenated in glacial acetic acid over palladium, absorbs 1 mole of hydrogen, yielding dihydroheliettin (II) $C_{19}H_{24}O_4$, m.p. 150·5–151°. The UV absorption (Fig. 1) is very similar to that of heliettin, showing that the double bond reduced is isolated from the chromophoric system. The IR spectrum is also very similar to that of heliettin.



I



II

The strong fluorescence and the UV spectrum suggest that heliettin is a coumarin, with, as usual, an oxygen atom at the 7-position (cf. Fig. 1). The IR absorption bands at 1710 and 1630 cm^{-1} also indicate the presence of a coumarin nucleus. This was confirmed by heating heliettin with dilute aqueous sodium hydroxide: it is insoluble

[1] Part XXI: R. A. Labriola and D. Giacopello, *Anales Asoc. Quim. Argentina* **54**, 15 (1966).

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[3] These authors gratefully acknowledge research fellowships from the University of Buenos Aires and the Consejo Nacional de Investigaciones Científicas y Técnicas of Argentina.

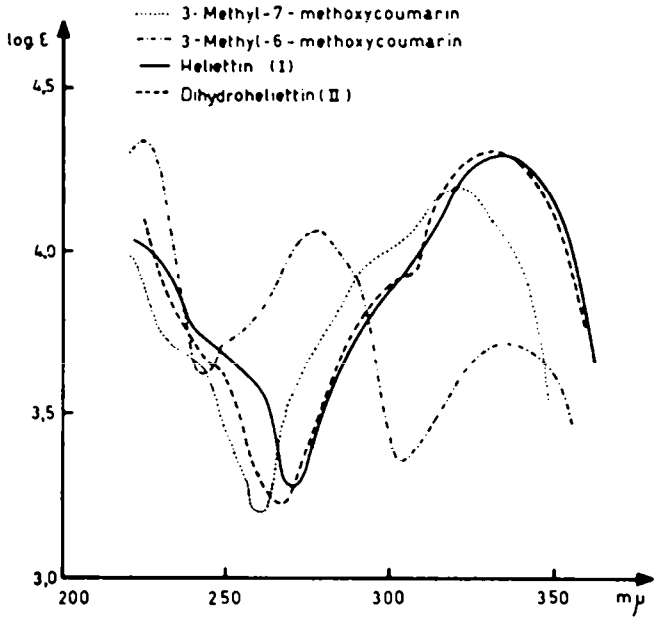
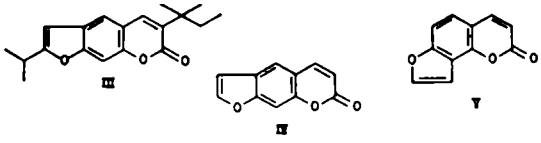


FIG. 1

in the cold, but after prolonged heating it yields a yellow solution from which the original substance can be recovered on acidification.

The IR spectra of heliettin and dihydroheliettin show that a OH group is present in both substances. This was confirmed by the preparation of acetyldihydroheliettin. Since both substances are insoluble in cold alkali, the OH group is probably non-phenolic. The negative result of a Jones oxidation (*vide infra*) indicate a tertiary alcohol.

Since from *Balfourodendron riedelianum*, belonging to the same subtribe (Pteleinae) as Helietta, several alkaloids have been isolated which possess an α-hydroxyisopropyl-dihydrofuran fragment, for instance balfourodine[4] (XIX) and ribalinium,[5] it was considered possible that heliettin could contain such fragment. In order to confirm this hypothesis, and to ascertain whether the furan nucleus is fused in a linear or angular fashion to the coumarin, dihydroheliettin was dehydrated by refluxing in benzene with P_2O_5.[6] The reaction gave dihydroanhydroheliettin, $C_{19}H_{22}O_3$, m.p. 101·5–102·5° (III). Comparison of its UV spectrum with those of psoralene[7] (IV) and angelicin[8] (V) (Fig. 2), showed that dihydroheliettin contains a furan ring, probably fused linearly to the coumarin nucleus.



III IV V

[4] H. Rapoport and K. G. Holden, *J. Am. Chem. Soc.* **81**, 3738 (1959); **82**, 4395 (1960).
[5] R. A. Corral and O. O. Orazi, *Tetrahedron* **21**, 909 (1965).
[6] A. Chatterjee and S. S. Mitra, *J. Am. Chem. Soc.* **71**, 606 (1949).
[7] E. C. Horning and D. B. Reisner, *J. Am. Chem. Soc.* **72**, 1516 (1950).
[8] C. Caporale and A. Cingolani, *Rend. Ist. Sup. Sanità, Roma* **21**, 943 (1958).

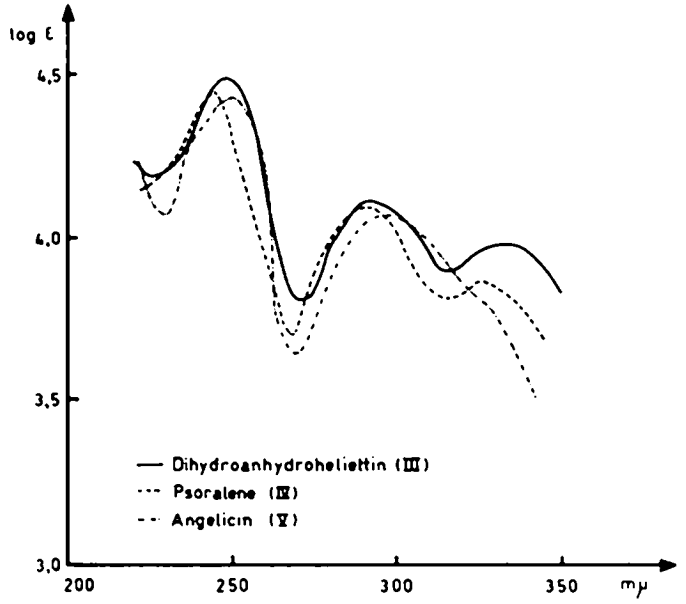
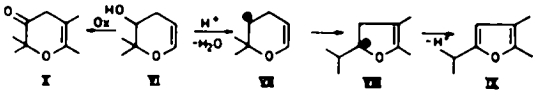


FIG. 2

That the furan ring was not produced by an acid-catalyzed rearrangement of a 2,2-dimethyl-3-hydroxydihydropyran ring (VI–IX), was proved by an attempted



Jones oxidation[9] of dihydroheliettin, in which 96% of the starting material was recovered. The secondary OH group of VI is very easily oxidized to the ketone X under such conditions, as in the oxidation of jatamansinol (XII) to jatamansinone.[10] The NMR spectra of heliettin and dihydroheliettin provided further evidence of the presence of a dihydrofuran nucleus and confirmed its linear attachment.

The first clue to the structure of the C_5H_9 unsaturated isoprenoid side chain, came from a modified Lemieux-Rudloff test,[11] in which the production of formaldehyde indicated the terminal position of the heliettin non-conjugated double bond. The structure and point of attachment of the side chain was ascertained by analysis of the NMR spectra of heliettin and dihydroheliettin, and further confirmed by chemical methods.

In the NMR spectra of coumarins, the protons on carbon atoms 3 and 4 give doublets ($J = 10$ c/s) at $\delta = 5{\cdot}93$–$6{\cdot}46$ and $7{\cdot}65$–$8{\cdot}03$ respectively.[12] In the NMR spectra of heliettin and dihydroheliettin (Fig. 3), the first signal is absent, and a singlet appears at $\delta = 7{\cdot}45$ (1 H), indicating that the side chain is bonded to the coumarin

[9] K. Bowden, J. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.* 39 (1946).

[10] S. N. Shanbag, C. K. Mesta, M. L. Maheshwari, S. K. Paknikar and S. C. Bhattacharyya, *Tetrahedron* **20**, 2605 (1964).

[11] R. Lemieux and E. von Rudloff, *Canad. J. Chem.* 33, 1701 (1955).

[12] S. S. Dharmatti, C. Govil, C. R. Kenekar, C. L. Khetrapal and Y. P. Virmani, *Proc. Indian Acad. Sci.* A56, 71 (1962); H. R. Arthur and W. D. Ollis, *J. Chem. Soc.* 8910 (1963).

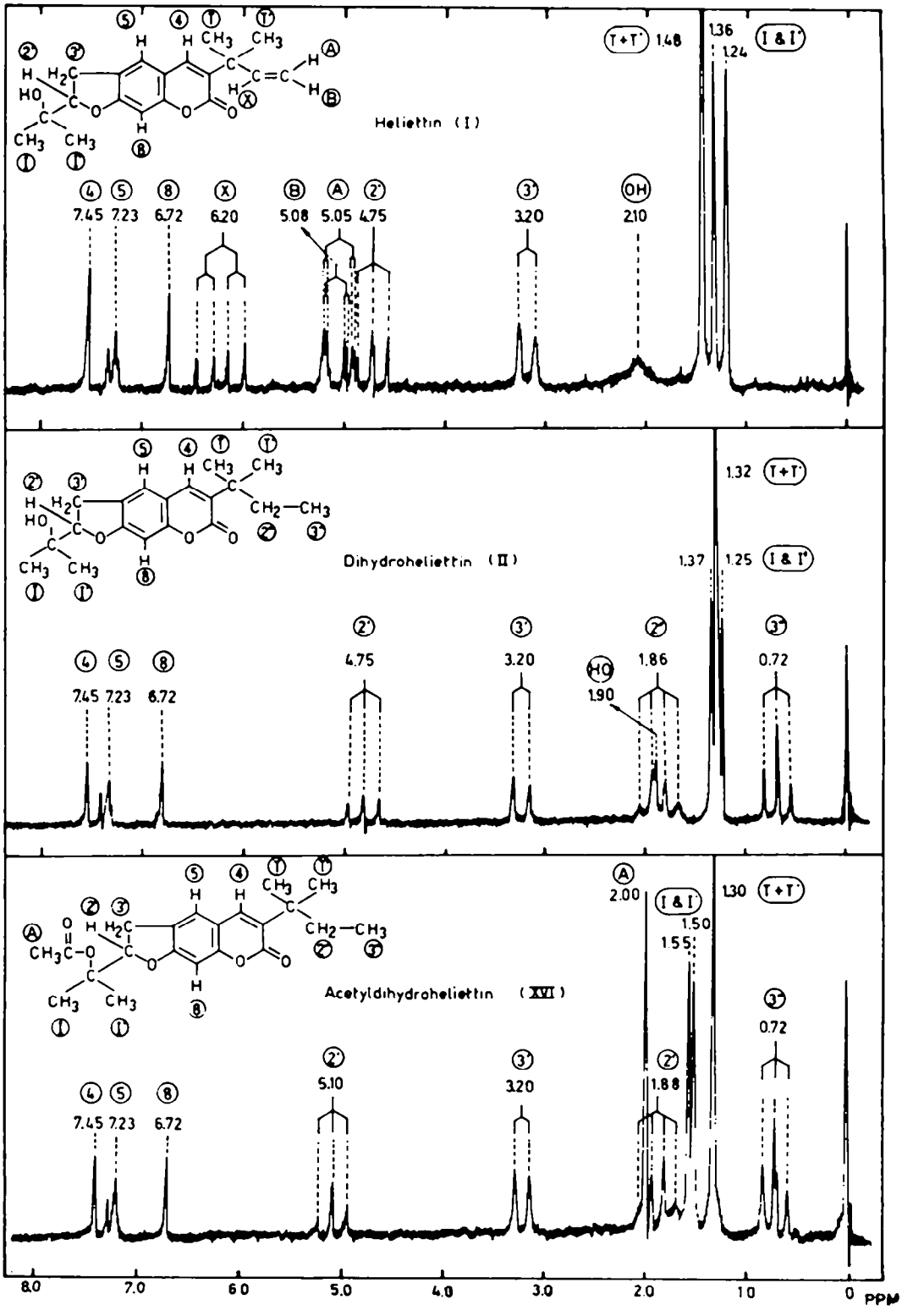
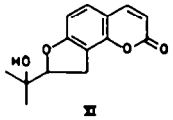

Heliettin (I)
Dihydroheliettin (II)
Acetyldihydroheliettin (XVI)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
ppm

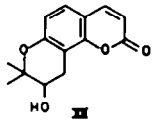
FIG. 3

nucleus through carbon 3. In the aromatic zone of both spectra there are two other singlets: a broad one at $\delta = 7{\cdot}23$ (1H) and another at $\delta = 6{\cdot}72$ (1H), which may be assigned to protons 5 and 8 respectively. The first signal is somewhat broadened, probably by long range coupling with the methylene group 3', the second is displaced to relatively high fields by the *ortho* oxygen substitution. The absence of coupling between the aromatic signals confirms the linear attachment of the dihydrofuran nucleus. The NMR spectra of heliettin and dihydroheliettin have the following further signals in common, due to the substituted dihydrofuran ring: a triplet ($J = 9$ c/s) at $\delta = 4{\cdot}75$ (1H) due to the proton at 2'; a doublet ($J = 9$ c/s) at $\delta = 3{\cdot}22$ (2H) due to the benzylic protons at 3' (slightly broadened by long range coupling to proton 5); two sharp singlets at $\delta = 1{\cdot}36$ (3H) and $\delta = 1{\cdot}24$ (3H), due to the Me groups of the α-hydroxyisopropyl side chain. The hydroxyl proton gives a signal at $\delta = 2{\cdot}00$ (1H).

The NMR spectral data can differentiate clearly between an α-hydroxyisopropyl-dihydrofuran nucleus as present in heliettin or columbianetin[13,14] (XI), and a 2,2-dimethyl-3-hydroxydihydropyran, as present in jatamansinol[10] (XII) or 3'-hydroxy-



XI



XII

3',4'-dihydroseselin.[13] In jatamansinol (XII) the proton on the methine carbon atom 3' gives a triplet signal at $\delta = 3{\cdot}95$, displaced nearly 50 c/s to higher fields than the heliettin 2' methine proton. The signal due to the methylene protons is, in the dihydrofuran nucleus a well defined doublet at $\delta = 3{\cdot}20$; in the other case it is an unresolved multiplet at $\delta = 3{\cdot}05$. On acylation of the OH group, the chemical shift of the methine proton is affected in a different manner.[13] In 3'-hydroxy-3',4'-dihydroseselin or jatamansinol, the triplet is shifted 67 c/s to lower fields, as expected of a secondary alcohol.[15] Instead, in acetyldihydroheliettin (XXII) (Fig. 3) as well as in columbianetin,[13] the corresponding signal is shifted only 22 c/s in the same direction. Another difference that could be of diagnostic value is the different way in which the signals of the *gem*-Me groups are affected on acylation: in dihydroheliettin they are shifted 13 c/s to lower fields, and in jatamansinol the shift is 6 c/s towards higher fields.

The remaining signals of the NMR spectra of heliettin and dihydroheliettin must come from the side chain attached to carbon 3, and must be different in both spectra on account of the saturation of the double bond. In the heliettin spectrum, an ABX system is clearly visible in the olefinic zone, which, on a first order analysis gives the following values: $\delta_A = 5{\cdot}05$, $\delta_B = 5{\cdot}08$, $\delta_X = 6{\cdot}20$, $J_{AX} = 18{\cdot}0$ c/s, $J_{BX} = 10{\cdot}0$ c/s, $J_{AB} = 1{\cdot}0$ c/s. This system is typical of a vinyl group attached to a quaternary carbon atom.[16,17] A sharp singlet at $\delta = 1{\cdot}48$ (6H), due to two equivalent Me groups bonded

[13] R. E. Willette and T. O. Soine, *J. Pharm. Sci.* 53, 275 (1964).

[14] N. S. Bhacca, L. F. Johnson and J. N. Shoolery, *High Resolution NMR Spectra Catalog* Vol. I; No. 310, Varian Associates, Palo Alto, California (1962).

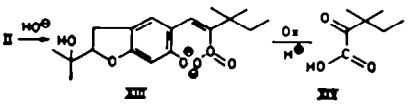
[15] L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, p. 55, Pergamon Press, London (1959).

[16] J. A. Pople, W. G. Schneider and H. J. Bernstein, *High Resolution Nuclear Magnetic Resonance* p. 241, McGraw-Hill, New York (1959).

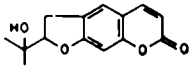
[17] M. L. Wolfrom, F. Komitsky, Jr., G. Fraenkel, J. H. Looker, E. E. Dickey, P. McWain, A. Thompson, P. M. Mundell and O. M. Windrath, *J. Org. Chem.* 29, 692 (1964).

to a quaternary carbon atom, allows the formulation of the C_5H_9 side chain as a 1,1-dimethylallyl group, and the structure of heliettin as I. The structure of the side chain is confirmed by the NMR spectrum of dihydroheliettin (Fig. 3). The ABX system in the olefinic zone has disappeared, and instead the group of bands typical of an Et group bonded to a quaternary carbon atom is visible as a quartet at $\delta = 1{\cdot}82$ (2H) ($J = 7$ c/s), and a triplet at $\delta = 0{\cdot}72$ (3H) ($J = 7$ c/s). The signal due to the *gem*-Me groups is shifted slightly, to $\delta = 1{\cdot}32$ (6H). Dihydroheliettin can be represented by structure II.

The structure of the side chain was further confirmed by potassium permanganate oxidation of dihydroheliettin in alkaline solution, from which 2-keto-3,3-dimethylvaleric acid (XIV) was obtained, identified through its Me ester and phenylhydrazone with an authentic sample prepared by synthesis.[18]



XIII XIV



XV

Heliettin has no optical rotation, either measured with the D sodium line or with the 546·1 mμ mercury line, and gives a flat ORD curve. As the carbon atom 2′ of the dihydrofuran ring is assymmetric, it must be a racemic modification. The only other known example of a racemic natural coumarin is inophyllolide, isolated from *Calophyllum inophyllum*.[19] The fact that, also exceptionally, both enantiomers of the very similar coumarin XV, nodakenetin[20] and marmesin,[6] have been found in nature, is worthy of mention.

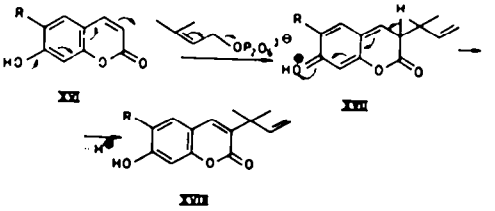
Three further points in the structure and reactivity of heliettin deserve brief comment.

Firstly, the 1,1-dimethylallyl side chain, found up to now only in two other natural products, echinulin[21] and macluraxanthone.[17]

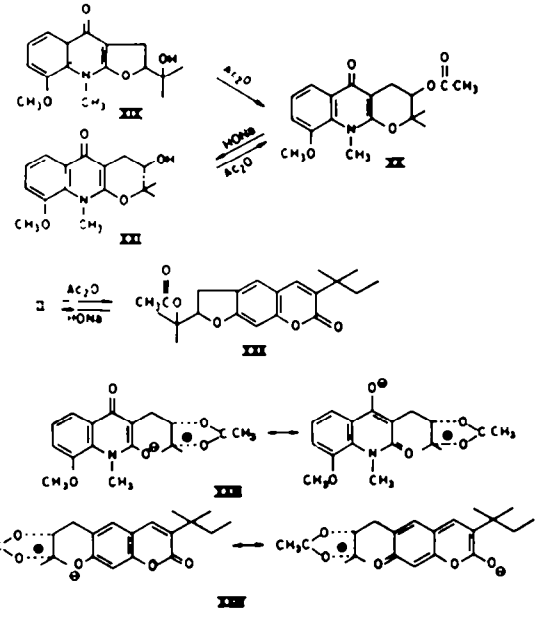
Secondly, the attachment of the isoprenoid side chain on carbon 3. The only other natural coumarins carrying an alkyl substituent on that position are ammoresinol[22] and ferulenol.[23] Both are 4-hydroxy-coumarins (benzotetronic acids), whose properties differ considerably from those of the other coumarins. The C-isoprenylation of phenolic compounds is generally believed to occur by an attack of γ,γ-dimethylallyl pyrophosphate on a highly anionoid position of the molecule.[24] The introduction of the 1,1-dimethylallyl side chain on the carbon 3 of heliettin, which lacks the *ortho*

[18] B. Fischer and B. Grützner, *Ber. Dtsch. Chem. Ges.* **26**, 1646 (1893).
[19] J. Polonsky and R. Toubiana, *C.R. Acad. Sci. Paris* **242**, 2877 (1956).
[20] J. Arima, *J. Chem. Soc. Japan* **48**, 88 (1927).
[21] G. Casnati, A. Quilico and A. Ricca, *Gazz. Chim. Ital.* **93**, 349 (1963).
[22] E. Späth and F. Kesztler, *Ber. Dtsch. Chem. Ges.* **70**, 1255, 1679 (1937).
[23] S. Carboni, V. Malaguzzi and A. Marsili, *Tetrahedron Letters* 2383 (1964).
[24] W. D. Ollis and I. O. Sutherland, *Recent Developments in the Chemistry of Natural Phenolic Compounds* (Edited by W. D. Ollis) p. 79. Pergamon Press, London (1961).

OH group, must be due to an activation of that position by the relatively distant OH group on carbon 7 of a precursor (XVI–XVIII).



Thirdly, on treatment with hot acetic anhydride and pyridine, balfourodine gives an acetate (XX), identical with that obtained from isobalfourodine (XXI); and on saponification it gives isobalfourodine.[4] Acetylation of dihydroheliettin, either according to Rapoport and Holden,[4] or with trifluoroacetic anhydride and acetic acid at room temperature,[25] yields the same product which, on saponification affords dihydroheliettin. Thus, in this case, acetylation does not bring about the rearrangement of the α-hydroxyisopropyldihydrofuran fragment into a 2,2-dimethyl-3-hydroxydihydropyran one. The structure of acetyldihydroheliettin, $C_{21}H_{26}O_5$, m.p. 161·5–162·5°, NMR spectrum Fig. 3, can be represented by formula XXII. This different reactivity[26] can be explained by the second mechanism proposed by Rapoport and Holden,[4] in which the rearrangement occurs through the resonance stabilized bridged ion XXIII. A similar intermediate in dihydroheliettin (XXIV), must undoubtedly be much less stable.



EXPERIMENTAL

M.ps are uncorrected. Microanalyses were performed by Dr. B. B. de Deferrari and by Dr. A. Bernhardt, Mülheim, Germany. UV spectra were determined in EtOH in a Beckman DU

[25] J. I. DeGraw, Jr., M. D. Bowen and W. A. Bonner, *Tetrahedron* **19**, 19 (1963).

[26] cf. F. M. Dean, *Naturally Occurring Oxygen Ring Compounds* p. 542. Butterworths, London (1963).

spectrophotometer. IR spectra were measured in a Perkin-Elmer 137B instrument, in Chf soln. NMR spectra were determined in $CDCl_3$ soln in a Varian A-60 spectrometer, with TMS as internal standard. TLC was performed with silica gel "G" (Merck), and the following solvent systems: light petroleum–AcOEt 100:3 (A), toluene–ethyl formate–formic acid 5:4:1 (B), Chf–MeOH 9:1 (C).

Heliettin (I)

The dried and powdered bark of *Helietta longifoliata* Britt. (3·0 kg) was extracted continuously for 3 days with pet. ether (b.p. 60–70°). The extract was concentrated to 500 ml and left overnight at 4°. The ppt which formed was recrystallized from benzene and then from isopropyl ether–isopropanol 3:1, giving colorless needles (1·32 g, 0·44% of dry bark), m.p. 165–166°, $[\alpha]_D^{20}$ ±0·0°, $[\alpha]_{546.1}^{20}$ ±0·0° (*c*, 2·1, chf), ORD curve: ±0° up to 380 mμ (*c*, 3·0, chf); UV spectrum: (Fig. 1); the NMR spectrum: Fig. 3; R_f 0·19 (A), 0·52 (B). (Found: C, 72·58; H, 7·06. $C_{19}H_{22}O_4$ requires: C, 72·59; H, 7·05%.)

Dihydroheliettin (II)

A soln of heliettin (497 mg) in AcOH (25 ml) was added to a suspension of prereduced $PdCl_2$ on carbon (10% Pd) (102 mg) in the same solvent (5 ml), and hydrogenated at room temp and atm. press. After 1 mole of H was absorbed (1 hr), the catalyst was filtered off, the soln diluted with ethyl ether (200 ml) and washed with water and sat $NaHCO_3$aq to eliminate the acid. The ethereal extract was dried (Na_2SO_4) and the solvent evaporated, leaving a residue (466 mg), which crystallized from isopropyl ether–MeOH, m.p. 150·5–151°; UV spectrum: λ_{max} 335 mμ (log ε_{max} 4·30) (Fig. 1); the NMR spectrum is shown in Fig. 3; R_f 0·22 (A), 0·56 (B). (Found: C, 72·16; H, 7·56. $C_{19}H_{24}O_4$ requires: C, 72·12; H, 7·65%.)

Dihydroanhydroheliettin (III)

To a soln of dihydroheliettin (503 mg) in dry benzene (100 ml), P_2O_5 (5·0 g) was added, and the mixture refluxed 5 hr. It was then filtered through glass wool and concentrated to dryness, giving a crystalline residue (363 mg) that recrystallized from MeOH–water, m.p. 101–102°; UV spectrum: λ_{max} 250, 295 and 335 mμ (log ε_{max} 4·51, 4·11 and 3·98 respectively) (Fig. 2). NMR spectrum: four singlets at δ = 7·62 (1H), 7·55 (1H), 7·38 (1H) and 6·42 (1H), due to the protons in positions 4′, 5, 8 and 3′ respectively; a multiplet centered at δ = 3·1 (1H) (J = 7 c/s) and a doublet at δ = 1·38 (6H) (J = 7 c/s), due to the methine and Me protons of the isopropyl side chain; a quartet at δ = 1·90 (2H) (J = 7 c/s) and a triplet at δ = 0·78 (3H) (J = 7 c/s), due to the Et group bonded to the quaternary carbon atom of the *t*-amyl side chain, and a singlet at δ = 1·38 (6H) due to the two Me groups bonded to the same carbon. R_f 0·76 (A), 0·70 (B). (Found: C, 76·31; H, 7·55. $C_{19}H_{22}O_3$ requires: C, 76·48; H, 7·43%.)

Acetyldihydroheliettin (XXII)

(a) Dihydroheliettin (53 mg) was dissolved in a mixture of AcOH (28 mg) and trifluoroacetic anhydride (112 mg) and left at room temp 1 hr. Sat $NaHCO_3$aq (6 ml) was then added, and the resulting suspension extracted with ethyl ether. The ether extract was dried (Na_2SO_4) and concentrated to dryness, leaving a residue (64 mg) which recrystallized from isopropyl ether, m.p. 161–162°. The NMR spectra is shown in Fig. 3. R_f 0·30 (A), 0·62 (B).

(b) A soln of dihydroheliettin (50 mg) in pyridine (0·5 ml) and Ac_2O (2·5 ml), was refluxed 6 hr. It was then cooled, and $NaHCO_3$aq added. The suspension was extracted with ethyl ether, the ethereal extracts washed with 2N HCl, dried (Na_2SO_4) and the solvent evaporated. The crystalline residue (53 mg) was recrystallized from isopropyl ether giving needles, m.p. 160–161°, whose IR and NMR spectra were identical with the previous product, mixed m.p.: 160–161°; R_f 0·30 (A), 0·62 (B) (Found: C, 70·79; H, 7·51. $C_{21}H_{26}O_4$ requires: C, 70·45; H, 7·32%.)

Hydrolysis of acetyldihydroheliettin. A soln of XXII (30 mg) in 5% methanolic KOH (4 ml) was refluxed 50 min. It was then cooled, diluted with the same volume of water, and acidified with conc. HCl. A ppt formed and was filtered off (29 mg), m.p. 150–151°. Its IR spectrum is identical with that of dihydroheliettin. R_f 0·22 (A), 0·56 (B).

Test for methylene and isopropylidene groups. The substance (6 mg) was dissolved in a mixture of water (7 ml) and pyridine (2 ml). To the soln 0·02M $NaIO_4$ (10 ml) and 0·005M $KMnO_4$ (1 ml)

was added, and left 30 min at room temp. Aliquots (1 ml) of this soln (S) were employed for testing the presence of formaldehyde and acetone. Formaldehyde: to 1 ml of (S) 1 ml of a soln of 200 mg of chromotropic acid in 100 ml 6N H_2SO_4 was added, and the mixture heated 60 min on a steam bath. A violet colour indicates a positive result. Cinchonine and heliettin: positive; coumarin and dihydroheliettin: negative. Acetone: to 1 ml of (S) 10N NaOH (1 ml) and a 20% soln of salicylaldehyde in EtOH (1 ml) was added, and the soln heated 30 min on a water bath. A deep red color indicates a positive result. Mesityl oxide: positive; heliettin and dihydroheliettin: negative.

Attempted Jones' oxidation of dihydroheliettin. A soln of III (62 mg) in acetone (20 ml) was treated with Jones' reagent[9] (0·1 ml) at 0° for 1½ hr. Water (30 ml) was then added, and the acetone evaporated. The aqueous phase was extracted with chf. After drying (Na_2SO_4), the solvent was removed and the residue (60 mg) crystallized from isopropyl ether–MeOH, m.p. 150–151°. IR spectrum identical with that of III, mixed m.p. 150–151°. R_f 0·21 (A), 0·56 (B).

1-*Keto*-2,2-*dimethylvaleric acid* (XIV). Dihydroheliettin (700 mg) was dissolved in 10% NaOHaq (25 ml) by refluxing 4 hr. Water was added (250 ml), the soln brought to 70°, and a 2% $KMnO_4$aq added dropwise until the color persisted 15 min. The suspension was cooled and the ppt MnO_2 dissolved with SO_2. The acidified soln was extracted continuously with ethyl ether, and the ether phase extracted in turn with 5% $NaHCO_3$aq, which was then acidified with conc. HCl and extracted with ethyl ether. After drying (Na_2SO_4), the solvent was removed at atm press, leaving a residue (315 mg) that was dissolved in chf and chromatographed on silica gel (50 g). Elution with chf gave a middle fraction of R_f 0·35 (C), which on evaporation of the solvent gave an oily residue (51·5 mg). This product gave a phenylhydrazone, m.p. 145–148°; phenylhydrazone of a synthetic sample of 1-keto-2,2-dimethyl valeric acid, m.p. 145–148°, mixed m.p. 145–148°. The IR spectra of both phenylhydrazones are identical. The IR spectra of the methyl esters are also identical.

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